

We claim:

1. A peptide compound of the formula (I) [SEQ. ID. NO. 4]:

Xaa₁ Xaa₂ Xaa₃ Gly Xaa₅ Xaa₆ Xaa₇ Xaa₈ Xaa₉ Xaa₁₀
Xaa₁₁ Xaa₁₂ Xaa₁₃ Xaa₁₄ Xaa₁₅ Xaa₁₆ Xaa₁₇ Ala Xaa₁₉ Xaa₂₀
Xaa₂₁ Xaa₂₂ Xaa₂₃ Xaa₂₄ Xaa₂₅ Xaa₂₆ Xaa₂₇ Xaa₂₈-Z₁; wherein

Xaa₁ is His, Arg or Tyr;

Xaa₂ is Ser, Gly, Ala or Thr;

Xaa₃ is Asp or Glu;

Xaa₅ is Ala or Thr;

Xaa₆ is Ala, Phe, Tyr or naphthylalanine;

Xaa₇ is Thr or Ser;

Xaa₈ is Ala, Ser or Thr;

Xaa₉ is Asp or Glu;

Xaa₁₀ is Ala, Leu, Ile, Val, pentylglycine or Met;

Xaa₁₁ is Ala or Ser;

Xaa₁₂ is Ala or Lys;

Xaa₁₃ is Ala or Gln;

Xaa₁₄ is Ala, Leu, Ile, pentylglycine, Val or Met;

Xaa₁₅ is Ala or Glu;

Xaa₁₆ is Ala or Glu;

Xaa₁₇ is Ala or Glu;

Xaa₁₉ is Ala or Val;

Xaa₂₀ is Ala or Arg;

Xaa₂₁ is Ala or Leu;

Xaa₂₂ is Phe, Tyr or naphthylalanine;

Xaa₂₃ is Ile, Val, Leu, pentylglycine, tert-butylglycine
or Met;

Xaa₂₄ is Ala, Glu or Asp;

Xaa₂₅ is Ala, Trp, Phe, Tyr or naphthylalanine;

Xaa₂₆ is Ala or Leu;

Xaa₂₇ is Ala or Lys;

Xaa₂₈ is Ala or Asn;

Z₁ is -OH,

-NH₂,

Gly-Z₂,

Gly Gly -Z₂

Gly Gly Xaa₃₁-Z₂,

Gly Gly Xaa₃₁ Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂ or

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂;

wherein

Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine and N-alkylalanine; and

Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₅, Xaa₆, Xaa₈, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉, Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇, and Xaa₂₈ are Ala; and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein Xaa₁ is His or Tyr.

3. A compound according to claim 2 wherein Xaa₁ is His.
4. A compound according to claim 2 wherein Xaa₂ is Gly.
5. A compound according to claim 4 wherein Xaa₁₄ is Leu, pentylglycine or Met.
6. A compound according to claim 5 wherein Xaa₂₅ is Trp or Phe.
7. A compound according to claim 6 wherein Xaa₆ is Phe or naphthylalanine; and Xaa₂₂ is Phe or naphthylalanine; Xaa₂₃ is Ile or Val.
8. A compound according to claim 7 wherein Z₁ is -NH₂.
9. A compound according to claim 7 wherein Xaa₃₁, Xaa₃₆, Xaa₃₇, and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.
10. A compound according to claim 9 wherein Z₂ is -NH₂.
11. A compound according to claim 1 wherein Xaa₂ is Gly.
12. A compound according to claim 1 wherein Xaa₁₄ is Leu, pentylglycine or Met.
13. A compound according to claim 1 wherein Xaa₂₅ is Trp or Phe.
14. A compound according to claim 1 wherein Xaa₆ is Phē or naphthylalanine; Xaa₂₂ is Phe or naphthylalanine; Xaa₂₃ is

Ile or Val.

15. A compound according to claim 1 wherein Z_1 is $-NH_2$.

16. A compound according to claim 1 wherein Xaa_{31} , Xaa_{36} , Xaa_{37} and Xaa_{38} are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.

17. A compound according to claim 1 wherein Z_2 is $-NH_2$.

18. A compound according to claim 1 which has an amino acid sequence selected from SEQ. ID. NOS. 5 to 65.

19. A peptide compound of the formula (I) [SEQ. ID. NO. 4]:

Xaa_1 Xaa_2 Xaa_3 Gly Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10}
 Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} Xaa_{17} Ala Xaa_{18} Xaa_{19}
 Xaa_{20} Xaa_{21} Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25} Xaa_{26} Xaa_{27} $Xaa_{28}-Z_1$;

wherein

Xaa_1 is His or Arg;

Xaa_2 is Gly or Ala;

Xaa_3 is Asp or Glu;

Xaa_5 is Ala or Thr;

Xaa_6 is Ala, Phe or naphthylalanine;

Xaa_7 is Thr or Ser;

Xaa_8 is Ala, Ser or Thr;

Xaa_9 is Asp or Glu;

Xaa_{10} is Ala, Leu or pentylglycine;

Xaa_{11} is Ala or Ser;

Xaa₁₂ is Ala or Lys;
Xaa₁₃ is Ala or Gln;
Xaa₁₄ is Ala, Leu or pentylglycine;
Xaa₁₅ is Ala or Glu;
Xaa₁₆ is Ala or Glu;
Xaa₁₇ is Ala or Glu;
Xaa₁₉ is Ala or Val;
Xaa₂₀ is Ala or Arg;
Xaa₂₁ is Ala or Leu;
Xaa₂₂ is Phe or naphthylalanine;
Xaa₂₃ is Ile, Val or tert-butylglycine;
Xaa₂₄ is Ala, Glu or Asp;
Xaa₂₅ is Ala, Trp, or Phe;
Xaa₂₆ is Ala or Leu;
Xaa₂₇ is Ala or Lys;
Xaa₂₈ is Ala or Asn;
Z₁ is -OH,
-NH₂,
Gly-Z₂,
Gly Gly -Z₂,
Gly Gly Xaa₃₁-Z₂,
Gly Gly Xaa₃₁ Ser-Z₂,
Gly Gly Xaa₃₁ Ser Ser-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂ or Gly Gly
Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂;
Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected
from the group consisting of Pro, homoproline,
thioprolin and N-methylalalanine; and
Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₅, Xaa₆, Xaa₈, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉, Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇ and Xaa₂₈ are Ala; and pharmaceutically acceptable salts thereof.

20. A compound according to claim 19 which has an amino acid sequence selected from SEQ. ID. NOS. 6-19.

21. A composition comprising a compound of any of claims 1 to 19 in a pharmaceutically acceptable carrier.

22. A composition comprising a compound of claim 20 in a pharmaceutically acceptable carrier.

23. A method for the treatment of diabetes mellitus comprising the administration of a therapeutically effective amount of a compound according to claim 1.

24. A method for the treatment of diabetes mellitus comprising the administration of a therapeutically effective amount of a compound according to claim 18.

25. A method for the treatment of diabetes mellitus comprising the administration of a therapeutically effective amount of a compound according to claim 19.

26. A method for the treatment of diabetes mellitus comprising the administration of a therapeutically effective amount of a compound according to claim 20.

27. The method of claim 23 further comprising the administration of a therapeutically effective amount of an insulin.

28. The method of claim 24 further comprising the administration of a therapeutically effective amount of an insulin.

29. The method of claim 25 further comprising the administration of a therapeutically effective amount of an insulin.

30. The method of claim 26 further comprising the administration of a therapeutically effective amount of an insulin.

31. A method for the treatment of a hyperglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 1.

32. A method for the treatment of a hyperglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 18.

33. A method for the treatment of a hypoglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 19.

34. A method for the treatment of a hypoglycemic condition in a mammal comprising the step of administering a therapeutically effective amount of a compound according to claim 20.

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35. A peptide compound of the formula (II) [SEQ. ID. NO. 66]:

Xaa₁ Xaa₂ Xaa₃ Gly Xaa₅ Xaa₆ Xaa₇ Xaa₈ Xaa₉ Xaa₁₀
Xaa₁₁ Xaa₁₂ Xaa₁₃ Xaa₁₄ Xaa₁₅ Xaa₁₆ Xaa₁₇ Ala Xaa₁₉ Xaa₂₀
Xaa₂₁ Xaa₂₂ Xaa₂₃ Xaa₂₄ Xaa₂₅ Xaa₂₆ X_{1-Z_i}; wherein

Xaa₁ is His, Arg or Tyr or 4-imidazopropionyl;
Xaa₂ is Ser, Gly, Ala or Thr;
Xaa₃ is Asp or Glu;
Xaa₅ is Ala or Thr;
Xaa₆ is Ala, Phe, Tyr or naphthylalanine;
Xaa₇ is Thr or Ser;
Xaa₈ is Ala, Ser or Thr;
Xaa₉ is Asp or Glu;
Xaa₁₀ is Ala, Leu, Ile, Val, pentylglycine or Met;
Xaa₁₁ is Ala or Ser;
Xaa₁₂ is Ala or Lys;
Xaa₁₃ is Ala or Gln;
Xaa₁₄ is Ala, Leu, Ile, pentylglycine, Val or Met;
Xaa₁₅ is Ala or Glu;
Xaa₁₆ is Ala or Glu;
Xaa₁₇ is Ala or Glu;
Xaa₁₉ is Ala or Val;
Xaa₂₀ is Ala or Arg;
Xaa₂₁ is Ala, Leu or Lys-NH^e-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkylkanoyl;
Xaa₂₂ is Phe, Tyr or naphthylalanine;
Xaa₂₃ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
Xaa₂₄ is Ala, Glu or Asp;
Xaa₂₅ is Ala, Trp, Phe, Tyr or naphthylalanine;

Xaa₂₆ is Ala or Leu;

X₁ is Lys Asn, Asn Lys, Lys-NH^c-R Asn, Asn Lys-NH^c-R, Lys-NH^c-R Ala, Ala Lys-NH^c-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkylalkanoyl

Z₁ is -OH,

-NH₂,

Gly-Z₂,

Gly Gly-Z₂

Gly Gly Xaa₃₁-Z₂,

Gly Gly Xaa₃₁ Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂ or

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂; wherein

Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently

selected from the group consisting of Pro,

homoproline, 3Hyp, 4Hyp, thioproline,

N-alkylglycine, N-alkylpentylglycine and

N-alkylalanine; and

Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₅, Xaa₆, Xaa₈, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉, Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, and Xaa₂₆ are Ala; and pharmaceutically acceptable salts thereof.

36. A compound according to claim 35 wherein Xaa₁ is His, Tyr or 4-imidazopropionyl.

37. A compound according to claim 36 wherein Xaa₁ is His.

38. A compound according to claim 36 wherein Xaa₁ is 4-imidazopropionyl.

39. A compound according to claim 35 wherein Xaa₂ is Gly.

40. A compound according to claim 35 wherein Xaa₁₄ is Leu, pentylglycine or Met.

41. A compound according to claim 35 wherein Xaa₂₅ is Trp or Phe.

42. A compound according to claim 35 wherein Xaa₆ is Phe or naphthylalanine; Xaa₂₂ is Phe or naphthylalanine; and Xaa₂₃ is Ile or Val.

43. A compound according to claim 35 wherein Z₁ is -NH₂.

44. A compound according to claim 35 wherein Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.

45. A compound according to claim 35 wherein Z₂ is -NH₂.

46. A compound according to claim 35 wherein X₁ is Lys Asn, Lys-NH^e-R Asn, or Lys-NH^e-R Ala where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl.

47. A compound according to claim 35 wherein Xaa₂₁ is Lys-NH^e-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkylkanoyl.

48. A compound according to claim 35 wherein said compound has an amino acid sequence selected from SEQ. ID. NOS. 67-74.

49. A composition comprising a compound of any of claims 35-47 in a pharmaceutically acceptable carrier.

50. A composition comprising a compound of claim 48 in a pharmaceutically acceptable carrier.